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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,152	10/14/2005	Antti Haapalinna	06257.0123	5038

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,152	HAAPALINNA ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) *9 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/08, 06/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to the amendment submitted on 06/18/08. Claims 1-10 and 12-15 are currently pending in the application, with claim 11 having being cancelled and claims 9 and 12-15 having been withdrawn. Accordingly, claims 1-8 and 10 and the elected species filed in the reply dated 11/30/07 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the Restriction Requirement has been fully considered. While Examiner agrees with applicant that Unity of Invention practice applies to the instant application, Examiner would like to point out that it was stated on the record in the previous Office Action that lack of unity was established since the special technical feature (i.e. drug abuse) was disclosed in the prior art. As a result, the restriction requirement was deemed proper and was made Final.

Applicant's argument that the instant application is fully enabled for the prevention of one or more withdrawal symptoms has been fully considered but is not found persuasive. Examiner respectfully points out that drug abuse typically entails withdrawal symptoms such as dysphoria, depression, anergia, fatigue, etc... as taught

by Murray et al., yet applicant provides no guidance or working examples demonstrating that administration of an alpha2-adrenoceptor antagonist **prevented** occurrence of the aforementioned withdrawal symptoms. Given the state of the art regarding the well-known withdrawal symptoms associated with drug abuse, it is incumbent upon applicant to demonstrate that the instant invention is able to "prevent" the aforementioned withdrawal symptoms. Additionally, given that applicant has not provided sufficient information or guidance regarding the subject matter of the claims (i.e. prevention) as to enable one skilled in the pertinent art to use the claimed invention as claimed, undue experimentation would have been needed to make and use the claimed invention. Moreover, in view of the definition of the term "to prevent" and absent of applicant's own limiting definition, such term was interpreted with the broadest reasonable interpretation which is "to keep from happening" or "to completely eradicate". Thus, in view of such definition and lack of guidance, applicant has failed to demonstrate that the aforementioned symptoms are prevented from happening or eradicated by administering an alpha2-adrenoceptor antagonist. As a result, claim 3 was found to be non-enabled for the prevention of one or more withdrawal symptoms and the rejection of claim 3 under 35 U.S.C. § 112, first paragraph is therefore maintained.

Applicant's traversal with respect to the rejection of claims 1-2 and 6-8 under 35 U.S.C. § 102 (b) has been fully considered but is not found persuasive. Examiner respectfully points out that applicant's arguments are directed to the newly amended claims and as therefore applicant's arguments are moot. Moreover, the claims as

previously presented recite a method for the treatment of physical dependence (i.e. drug abuse) and/or one or more withdrawal symptoms caused by discontinuation of the use of at least one psychostimulant agent in a mammal which comprises administration to the mammal an effective amount of a selective alpha2-adrenoceptor antagonist. Seiler et al. teach compounds of formula III which are selective for the alpha2c-adrenoceptor (see col. 3, lines 48-50) which can inhibit the effects of amphetamine and useful in treating depression (i.e. a withdrawal symptom associated with drug dependence). Murray, on the other hand, was provided as evidentiary support to show that depression is a withdrawal symptom of physical dependence of psychostimulants such as amphetamines. Consequently, Seiler et al. did indeed anticipate applicant's invention. However, in view of applicant's amendment, the rejection of claims 1-2 and 6-8 under 35 U.S.C. § 102 (b) is hereby withdrawn.

Applicant's argument with respect to Seiler and Murray who do not render obvious applicant's invention has been fully considered but is not found persuasive. The claims as previously presented recited the use of selective alpha2-andrenoceptor antagonists useful in treating depression (i.e. a withdrawal symptom of drug dependence) and in inhibiting the effects of amphetamines. Thus, one of ordinary skill would have found it obvious to administer the alpha2-adrenoceptor antagonists for the treatment of withdrawal symptoms of physical dependence in view of Seiler and Murray since Seiler et al. teach their use in alleviating depression and in inhibiting the effects of psychostimulants such as amphetamines. As for applicant's arguments that the

compounds of Seiler et al. have effects on other receptors while the compounds of the instant application do not affect those systems, such arguments are moot as the claims did not recite preferred selectivity of the compounds. Moreover, applicant argues that the aforementioned compounds are used for the preferred embodiments of depression while atipamezole is ineffective in a rat depression model. Again, applicant's arguments are moot and unpersuasive as independent claim 1 did not recite the alpha2-adrenoceptor antagonist as atipamezole. Consequently, Seiler et al. in view of Murray do indeed render obvious applicant's invention.

Applicant's argument with respect to Seiler, Murray, and Sallinen who do not render obvious applicant's invention has been fully considered but again is not found persuasive. In particular, Sallinen et al. teach that α-2 receptors play a modulatory role in depression (see abstract and pg. 3035, left col., paragraph 1) and further teach compounds that are **subtype non-selective**-α-2c adrenoceptor antagonists (see pg. 3038, paragraph 3) as therapeutically useful in disorders associated with enhanced startle responses, sensorimotor gatting deficits and for drug withdrawal (see abstract). Sallinen et al. further teach that **subtype selective** α-2 adrenoceptor antagonists were not available (see pg. 3035, Introduction, right col. paragraph 2) and therefore teach atipamezole as a **subtype non-selective**-α-2-adrenoceptor antagonist and not that atipamezole is a non-selective α2-adrenoceptor antagonist. Moreover, applicant own specification teach that atipamezole is a selective alpha2-adrenoceptor antagonist (see pg. 4, lines 24-28). Thus, in view of the teachings of Sallinen et al. who teach that Sallinen et al. who teach that alpha-2 receptors play a role in depression and the fact

that Sallinnen et al. teach an alpha-2 adrenoceptor antagonists as useful in various disorders including drug withdrawal, and Murray et al. teach that drug withdrawal symptoms include depression, one of ordinary skill in the art would have found it obvious to administer atipamezole for treating withdrawal symptoms such as depression. Consequently, the rejection of claim 10 under 35 U.S.C. § 103 (a) was indeed proper. However, in view of applicant's amendment the rejection is hereby withdrawn.

For the foregoing reasons, the rejection of claim 3 was proper. However, in view of applicant's amendment, the following modified 112, first paragraph and 103 (a) Final rejections are being made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is being rejected for total lack of enablement. When claims 4-6, 8 and 10 depend from claim 3, the aforementioned claims are also rejected as a claim in a dependent form is construed to incorporate by reference all the limitations of the claim to which it refers. See M.P.E.P. 2164.08.

Claims 3-6, 8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method for the

prevention of the development of drug dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent in a mammal, which comprises administering to the mammal an effective amount of a selective alpha-2-adrenoceptor antagonist chosen from a selected group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. For example, after chronic drug abuse and cessation thereafter, patients typically develop withdrawal symptoms, a central nervous system response to the dependence on the drug (Murray, J. of Psych. 1998, pg. 231, paragraph 3, previously submitted). Consequently, prevention of withdrawal symptoms regardless of the severity is unlikely.

The instant claim is drawn to a method for the prevention of the development of dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent in a mammal, which comprises administering to the mammal an effective amount of a selective alpha-2-adrenoceptor antagonist selective from a group. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention.

Attention is directed to *In reWands,* 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or

unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method for the prevention of the development of dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent in a mammal, which comprises administering to the mammal an effective amount of a selective alpha-2-adrenoceptor antagonist selective from a group. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the predictable nature of the art since drug abuse is well studied in the prior art. As illustrative of the state of the art, the examiner cites the above fact that after chronic drug abuse and cessation thereafter, patients typically develop withdrawal symptoms, a central nervous system response to the dependence on the drug and therefore prevention of withdrawal symptoms regardless of the severity is highly unlikely.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prevention" as "to keep from happening or existing", i.e., to completely eradicate.

The claims are thus very broad insofar as they recite the "prevention" of the development of drug dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent, i.e., the complete eradication of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for a method for preventing the development of drug dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent.

4. The quantity of experimentation necessary

Because of the predictability of the art and the fact that drug dependence is well-studied in the prior art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed alpha-2 adrenoceptor antagonists could be predictably used to prevent development of drug dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement

requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation in order to determine if alpha-2 adrenoceptor antagonists claimed by applicant can prevent or forever hinder the development of drug dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent, with no assurance of success.

Genentech, 108 F.3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for the prevention of the development of dependence and/or one or more withdrawal symptoms caused by the discontinuation of the use of at least one psychostimulant agent in a mammal, which comprises administering to the mammal an effective amount of a selective alpha-2-adrenoceptor antagonist selective from a group is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 6-8, and 10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Murray (J. of Psych. 1998, Vol. 132, No.2, pgs. 227-237, previously submitted) in view of Aantaa (Bailliere's Clinical Anesthesiology, 2000, Vol. 14, No. 2, pgs. 285-292).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Murray teaches that amphetamines is accompanied by many withdrawal effects including depression, dysphoria, anergia, cravings, sleepiness and fatigue (pg. 228, 4th paragraph and pg. 230, 2nd and 3rd paragraphs). Importantly, Murray teaches that complete discontinuation of amphetamines leads to clinical depression in his human participants (pg. 230, 4th paragraph).

Murray does not specifically teach a method of treating one or more withdrawal symptoms with a selective alpha-2 adrenoceptor antagonist.

Aantaa teaches that alpha-2 adrenergic receptors, also called imidazoline receptors, selectively bind imidazoline structure, active and non-active of the alpha-2 adrenergic receptor (pg. 286, top section). Of the commonly used alpha-2 adrenoceptor antagonists, atipamezole is the most specific and selective of the alpha-2 adrenoceptor antagonists having an α2:α1 selectivity ratio of approximately 8500 (see pg. 286, top section). Importantly, Aantaa teaches that alpha-2 adrenoceptor antagonists can be used in a variety of potential therapeutic applications including increasing the release of neurotransmitters for the treatment of depression (see pg. 287, last paragraph).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the selective alpha2-adrenoceptor antagonist, atipamezole, of Aantaa to treat withdrawal symptoms of amphetamines since Murray teaches that chronic abuse of amphetamines cause depression and Aantaa teaches that alpha2-adrenoceptor antagonists can be useful in the treatment of depression. Given the teachings of Murray and Aantaa, one of ordinary skill would have been motivated to utilize atipamezole in treating the withdrawal symptoms of amphetamines with the reasonable expectation of providing a successful method treatment that is efficacious in treating deleterious symptoms in patients.

Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray (J. of Psych. 1998, Vol. 132, No.2, pgs. 227-237, previously submitted) in view of Aantaa (Bailliere's Clinical Anesthesiology, 2000, Vol. 14, No. 2, pgs. 285-292) as applied to claims 1-2, 6-8, and 10 above and in further view of Ward et al. (The Lancet, 1999, Vol. 353, pg. 221-226, previously submitted).

The Murray and Aantaa references are as discussed above and incorporated by reference herein. However, Murray and Aantaa references do not address discontinuing the use of the at least one psychostimulant or gradually reducing the at least one psychostimulant upon administration of the at least one alpha-2-adrenoceptor antagonist.

Ward et al. teaches that in methadone maintenance treatment a substitution of one opioid (i.e. psychostimulant) is used in place of another (i.e. discontinuation of the addictive psychostimulant) and that the goal of most programs is toward abstinence (i.e. complete discontinuation of drugs vs. instant claim 4) from all opioid drugs (see pg. 221, Methadone Maintenance Treatment (MMT) Section). Ward further teaches that abrupt cessation of methadone often results in a characteristic withdrawal syndrome and that detoxification from MMT is best achieved by a slow reduction in the dose of methadone administered (see instant claim 5 vs. pg. 223, Duration and Withdrawal from MMT Section, 2nd paragraph).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the modified method of treatment of Murray and Aantaa in

view of the knowledge of drug administration provided by Ward et al. to arrive at the method of applicant given that MMT treatment has long been the standard treatment in drug addiction. Given that Aantta teaches alpha2-adrenoceptor antagonists such as atipamezole for the treatment of depression, and Murray discloses that drugs such as amphetamines are accompanied by withdrawal symptoms including depression, and Ward discloses a proven method of administration for opioid addiction, one of ordinary skill would have been motivated to utilize the modified method of treatment of Murray and Aantaa in view of the knowledge of drug administration provided by Ward et al. with the reasonable expectation of providing a method that is effective and successful in treating withdrawal symptoms.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-5 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

09/24/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617